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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,124	04/28/2000	Ralph A. Nixon	50122/002003	3388

21559 7590 04/06/2004

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/560,124	NIXON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17,19,20,22,24-28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16,17,19,20,22,24 and 25* is/are allowed.

6)☒ Claim(s) *27,28 and 30* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 18, 2004 (hereinafter referred to as "the response") has been entered. Claims 16, 22, 27, and 30 have been amended. Claim 21 has been cancelled.

Accordingly, Claims 16, 17, 19, 20, 22, 24-28, and 30 remain pending in the instant application.

The rejection of Claims 16, 17, 19, 20, 22, 24, and 25 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to Claims 16 and 22. Claims 16 and 22 have been amended so that the claimed method is carried out *in vitro*.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on March 18, 2004 has been entered.

Claim Objections

Claim 26 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 26 fails to further limit independent Claim 22 from which it depends..

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28, and 30 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 3-6 of the Office Action mailed 7/8/02, on pages 3-6 of the Office Action mailed 3/25/03, and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for identifying a candidate compound as a compound that may be useful for the treatment of Alzheimer's disease. The method involves using a mouse stably expressing a transgene comprising a recombinant rab5 nucleic acid that increases activity of the endocytic pathway.

At page 8 of the response, Applicants argue that murine L cells expressing rab5 in vitro exhibit an increase in endocytic pathway activity. Applicants assert that the Examiner has provided no reason to doubt that the observed phenotype of a cell stably expressing rab5 *in vitro* would fail to correlate with the predicted phenotype of a cell expressing rab5 *in vivo*. On the contrary, six references have been cited which demonstrate that phenotype is unpredictable. As one example, the references demonstrate that an *in vivo* phenotype observed in one species is not even predictive of an *in vivo* phenotype associated with the same genetic modification in another closely related species (see Mullins et al., 1990; Hammer et al., 1990; Mullins et al., 1989; and Taurog et al., 1988).

At page 9 of the response, Applicants argue that the Examiner has failed to provide any evidence showing that the mode of expression, acute versus stable, would affect the predicted *in vivo* cellular phenotype. On the contrary, six references have been provided to support the finding that the phenotype

of a transgenic mouse is unpredictable. The references demonstrate that phenotype cannot be predicted *a priori* based on the particular genetic modification being proposed. Applicants argue that the transient overexpression of rab5 in mouse *in vivo* is consistent with the cellular phenotype observed in murine cells *in vitro*. However, the instant specification does not teach using somatic cell genetic modification to produce an *in vivo* model overexpressing rab5. Rather, the instant specification teaches making and using transgenic mice that have a germline genetic modification. Since germline genetic modifications in conventional transgenic mice exist from the earliest stages of embryogenesis throughout development, this early expression of the transgene can be expected to influence the phenotypes observed in the adult.

At page 10 of the response, Applicants argue that the specification suggests which promoters should be used to achieve neuron-specific gene expression. Applicants point to Example 4 of the specification at page 17. The Examiner acknowledges that several preferred promoters are discussed in the specification. However, given the unpredictability in the art of transgenic animals, disclosure of preferred promoters is not sufficient to overcome the unpredictability in the art. As evidenced by the references of record, there are numerous examples in the art where a hoped-for phenotype is not observed in a transgenic mouse "model."

Given the limited guidance in the specification, the lack of working examples for rab5 transgenic mice, the unpredictability in the transgenic art with regard to phenotype, one skilled in the art would have been required to engage in undue experimentation in order to practice the claimed method *in vivo* in transgenic mice.

Thus, the rejection is maintained for reasons of record.

Conclusion

Claims 16, 17, 19, 20, 22, 24, and 25 are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER